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Towards Understanding the Early Events in the Conformational Transition of Amyloid Beta Peptides

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It is experimentally known that oligomerization of amyloid beta peptides is accompanied by a conformational transition from mainly alpha or random coil to beta sheets. The aim of this study is to analyze and compare the spatial orientation of hydration water near the peptide surface during this conformational transition of amyloid-beta 42 (Ab42) and amyloid-beta 40 (Ab40) peptides. Therefore, molecular dynamics (MD) simulations of 100 ns length with explicit representation of solvent were performed for individual amyloid beta monomers. Analysis was based on the radial distribution function (RDF) of hydration water for individual residues and for respective secondary structure elements. In all cases, initial results suggest that, in accord with the literature, the RDFs reveal the presence of two solvation shells around polar residues. Variations in RDF in the first solvation shell were found to be consistent with the physiochemical properties of the amino acids and were independent of the secondary structure element. However, individual residues that belonged to the secondary structure segments undergoing conformational transitions showed significant redistribution of water density. Further investigations, such as dimer formation and analysis of the orientation of water molecules near peptide surfaces are necessary to clarify the role played by surrounding water in the assembly of such unstructured peptides.

1 Introduction

Recent experimental evidence has implicated the toxicity of soluble oligomers of amyloid beta peptides in Alzheimer's disease[1]. Given the metastable nature of these oligomers, it is hard to obtain experimental data for the early events taking place during the oligomerization of amyloid beta peptides. Computational simulation methods are, hence, needed to provide atomistic details of the early events in amyloid beta oligomerization and there is already a broad literature[2]. As water is known to play a key role in protein folding, structure, dynamics, specific interactions and ligand binding, in this preliminary study, we focus on the spatial organization of water molecules present in solvent surrounding the amyloid beta peptides[3]. Halle recently discussed the technical advancements employed in investigating the influence of protein on surrounding solvent molecules[4], while Helms[5] and Bizzarri[6] reviewed the computational studies aimed at studying protein-water interface and the properties of water near protein surfaces.

The primary aim of this study is to understand the effect of amino acid polarity and peptide secondary structure on the spatial organization of water in its surrounding. To this end two 100 ns MD simulations of Ab40 and Ab42 monomers, respectively, were carried out in explicit solvent. The results obtained from the analysis of radial distribution of water molecules in both the simulations are compared based on the physio-chemical properties of individual residues and the secondary structure composition of residues. Amyloid beta peptides were chosen for this study as they show a well characterized conformational transition and hence can be ideal candidates for studying the effect of secondary structure

elements on surrounding water[7]. The RDFs, MD simulation set up and the starting structure of the peptides is briefly described in section 2. We first discuss the conformational transitions before analyzing the RDFs obtained from both simulations in section 3. The results in section 3 are discussed based on the individual residues, secondary structure elements and with respect to the residues that undergo conformational transition during the course of the simulations. The results presented here are taken from an ongoing investigation and certainly more independent MD simulations need to be conducted to determine the statistical relevance of the results discussed.

2 Methods and Simulation Setup

The initial coordinates for the Alzheimer Ab42 and Ab40 peptides were obtained from the solution structures of the Ab42 peptide in an apolar microenvironment (PDB ID: 1iyt) and of Ab40 in a water-micelle environment (PDB ID: 1ba4), respectively. All standard MD simulations were carried out with the Gromacs package[8] using the GROMOS96 53a5 force field in the NPT ensemble at 300 K and periodic boundary conditions. The linear constraint solver (LINCS) method was used to constrain bond lengths, allowing an integration step of 2 fs. Electrostatic interactions were calculated with the Particle-Mesh Ewald algorithm. **RDFs** describe the ratio between the local density around a reference site r_P and the average density ρ of water molecules in the solution. Here, the terminal atoms of the functional groups of individual residues were considered as reference points r_P and the RDFs were calculated for both the water oxygens $[g_{PO}(r)]$ and water hydrogens $[g_{PH}(r)]$. The RDFs were computed for 1) all amino acids based on their polarity 2) all the amino acids belonging to the same secondary structure element. It is to be noted that in case 2, average RDFs were calculated over certain time intervals to account for the conformational transition taking place during the course of simulation. All residues in the two peptides, irrespective of their solvent exposed surface area, were considered for estimating RDFs. The RDFs were calculated using the g_rdf module of Gromacs[8]. The secondary structure analysis was performed based on DSSP[9].

3 Results and Discussion

We focus here on the effect of the peptide conformational transition on the spatial organization of water surrounding the peptide. First we report the conformational transitions occurring in the peptides during the simulations. In the case of Ab42 peptide, the second alpha helix comprising of residues 28-39 of the Ab42 peptide converted within 5 ns into several beta sheets connected via beta bridges. However, the central hydrophobic region (residues 16-21) remained mostly in 5-helical structure with few local transitions to alpha helical structure during the 100 ns simulation. The remaining residues 1-14 mainly adopted random coil structure and finally settled into a beta sheet conformation at about 40 ns. Also, at about 40 ns, residues 28-33 formed a beta sheet that remained stable until 100 ns. Residues 34-42 formed a beta sheet at about 85 ns that remained stable till the end of the simulation. However, it is to be noted that the beta sheet secondary structure might be favored by the force field applied. In vast contrast to Ab42, no beta sheets formed in the Ab40 peptide and most of the residues remained in random coil conformation for

most of the simulation duration. It is noteworthy to mention that before being replaced by random coil structure, the alpha helix comprising of residues 10-17 remained stable for about 60 ns. The remaining residues 15-36 underwent a conformational transition from alpha helix to random coil within the first few nanoseconds of simulation. Ab40 residues 20-25 and 31-34 remained in random coil structure for most of the duration and adopted a beta sheet structure at about 80 ns. Remarkably, the simulations presented here capture the beta sheet forming tendency of both the peptides. In particular, it is to be noted that Ab42 is considered to be more prone to fibril formation and the emergence of beta sheet structure is suggested to play a key role in its oligomerization[10]. However, the aim of this study is not to highlight this beta sheet formation but rather understand the fluctuations in (solvent) water surrounding the segments that undergoes conformation transition.

The RDFs $[g_{PH}(r)]$ and $[g_{PO}(r)]$ measuring water-hydrogen and water-oxygen density at given distance, respectively, were computed for the terminal atoms of the functional groups present in the two peptides. As expected, the spatial distribution of water was effected by the polarity of the amino acid residue. Two solvent shells were clearly observed for the polar and charged residues, while only one shell was formed around the apolar residues. The water density at the first solvation shell was found to be lower for the apolar residues ($A_{max} \sim 0.7$) as compared to the polar and charged ones ($A_{max} \sim 1.1$). Further, $[g_{PH}(r)]$ and $[g_{PO}(r)]$ values were compared to estimate the orientation of water molecules about the residues. As expected for hydrogen bond donors like ARG and LYS, the first maxima for $[g_{PH}(r)]$ ($r_{max} \sim 2.6$Å) was found to be shifted to a larger distance as compared to $[g_{PO}(r)]$ ($r_{max} \sim 2$Å), signifying the fact that water hydrogens point away from hydrogen bond donor molecules[11].

To investigate the effect of secondary structure transition on water distribution, we identified the residues that had undergone conformational transition and calculated $[g_{PH}(r)]$ and $[g_{PO}(r)]$ functions with reference to the $C\alpha$ atom of the respective residue. In summary, residues 20-25 and 31-34 were identified to have undergone structural transition from random coil to beta sheets in Ab40. In the case of Ab42, residues 1-5 (random coil to beta sheet), 20-24 (alpha helix to random coil) and 34-42 (random coil to beta sheet) were observed to have undergone structural transition. Analysis of RDFs revealed that the effect of structural transition on the water distribution was negligible when the whole segment that had undergone transition was considered. However, the RDFs calculated for individual residues within a given segment seemed to have significant perturbations. As an outlook for this ongoing research, we plan to further investigate these perturbations in water distribution due to secondary structure transition. Moreover, multiple MD simulations with different force fields need to be run to attain statistically relevant results.

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